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TITLE: Pathophysiologic Impact of Doxorubicin and Radiation Therapy on the Heart of Patients Treated for Breast Cancer

PRINCIPAL INVESTIGATOR: Lawrence B. Marks, M.D.

CONTRACTING ORGANIZATION: Duke University Medical Center
Durham, North Carolina 27710

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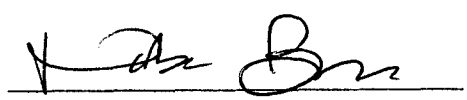

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Lawrence B. Marks, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Duke University Medical Center
Durham, North Carolina 27710

Marks@radonc.duke.edu

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13. ABSTRACT *(Maximum 200 Words)*

Purpose: To determine the incidence, dose/time-dependence, and functional significance of regional cardiac perfusion abnormalities in patients with left-sided breast cancer treated with radiation therapy (RT) with and without doxorubicin.

Methods: 114 patients underwent pre-RT single photon emission computed tomography (SPECT) cardiac perfusion imaging. Post-RT images were obtained in 97, 69, 65 and 28 patients 6, 12, 18, and 24 months post-RT. SPECT perfusion images were registered onto 3-dimensional (3D) RT dose distributions. The volume of heart in the RT field was quantified and the regional RT dose was calculated. Changes in regional and global cardiac function were assessed. **Results:** Overall, 49% of patients developed dose-dependent RT-induced perfusion defects. The incidence of defects increased with the volumes of heart irradiated, and may be more prevalent in African Americans (vs. Caucasians) and with chemotherapy (vs. RT alone). Perfusion defects were associated with changes in regional wall motion 20-40% of the time and possibly with the development of chest-pain. **Conclusions:** RT causes dose-dependent cardiac perfusion defects 6-24 months post-RT that appear to be associated with functional changes. The use of chemotherapy and African American race may increase this rate. Long-term follow-up is needed to assess whether these perfusion changes are transient or permanent and to determine if these findings are associated with changes in overall cardiac function and clinical outcome.

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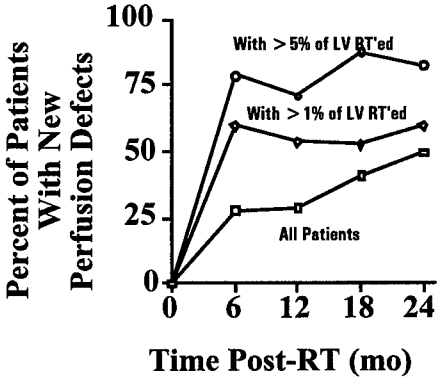
Introduction:

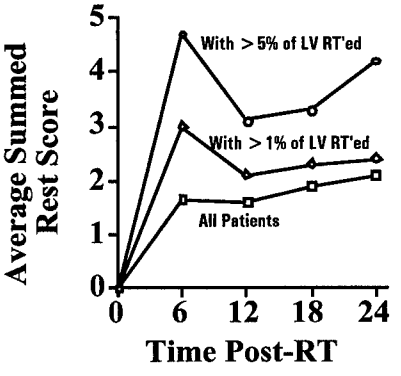
With the increasing use of radiotherapy in the management of primary breast cancer, there has been rising concern about the long-term side effects of radiation therapy. Some randomized series evaluating patients irradiated post-mastectomy report an excess number of cardiovascular deaths in the irradiated group (1). Additionally, radiotherapy to the heart in conjunction with the chemotherapy drug doxorubicin (Dox) appears to increase the risk of developing cardiac damage (2). New 3D radiation treatment planning tools provide the opportunity to know the 3D RT dose distribution in any tissue. Doses can be calculated for complex field arrangements and differences in tissue density may be considered (3). SPECT cardiac perfusion imaging provides a noninvasive assessment of myocardial perfusion and function. Advances in image registration allow us to superimpose the 3D dose distribution onto noninvasive nuclear medicine 3D cardiac imaging studies (4). Using 3D treatment planning tools and nuclear medicine perfusion imaging of the heart, we attempted to define the volume of left-ventricle in the RT treatment field, and correlate regions of post-RT perfusion changes with both the RT dose and the use of Dox-based chemotherapy.

Body: Data Presentation, Research Results:

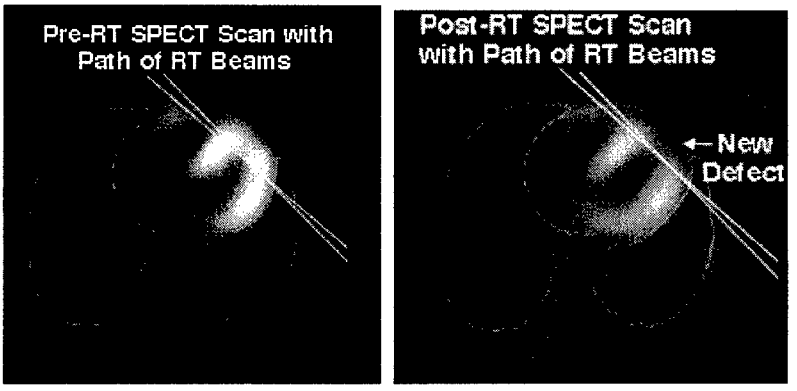
Between 1998-2002, we have enrolled 114 patients onto this clinical trial to assess RT-induced changes in regional and global cardiac function. The median age was 57 (range 33-82), 15 were AA, and 79 received chemotherapy prior to RT. Of these, 97, 69, 65, and 28 patients have follow-up data at 6, 12, 18 and 24 months post-RT, respectively. Not all patients are evaluable at all intervals due to patient attrition (19 refused to have FU scans); some FU scans are pending, and some scans have not yet been analyzed.

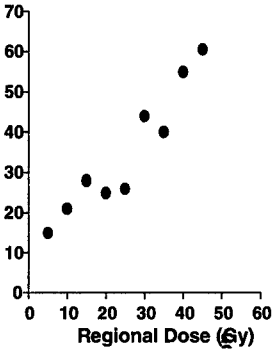
Visual evaluation of the SPECT scans (specific aim # 1 and 2): The presence and severity of defects were scored by a nuclear medicine radiologist based on a 12-segment model scoring system (summed rest score [SRS]; see Methods). The incidence of new perfusion defects for the entire population, and those whose percent of LV included in the RT field exceeded > 1% or > 5%, is shown for different post-RT intervals. Defects are more common in patients with larger volumes of the LV irradiated. In the patients with < 1% of their LV within the RT field, no new defects were detected. Similarly, the SRS scores over time are shown.





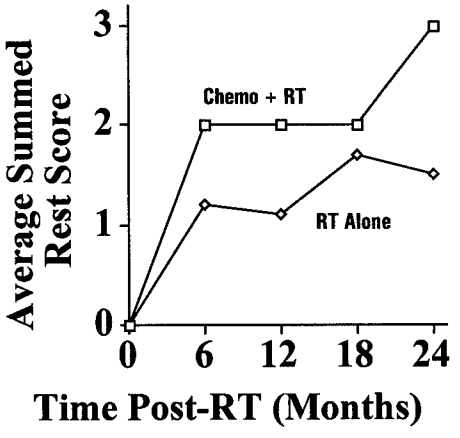
Quantitative analysis (specific aim # 1 and 2): The pre- and post-RT SPECT scans were registered with the 3D dose distribution from the planning system. Within each pixel of the LV, quantitative changes in regional perfusion were compared to the regional dose (see Methods). An example of a single patient's pre- and post-RT axial SPECT image is shown. There is a clear reduction in perfusion within the RT field on the post-RT image. The associated patient-specific dose response curve (DRC) is shown.



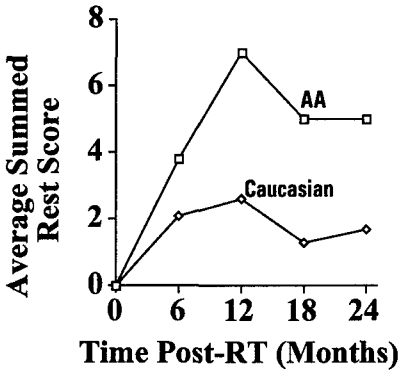


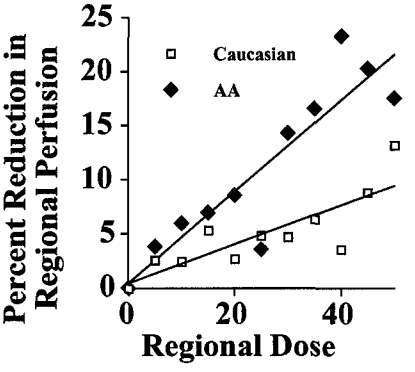
Similar data were generated for each patient at each follow-up evaluation. Population DRCs are calculated by pooling the data from multiple patients. The population 6-month DRC is shown. There is a clear dose-dependent reduction in regional perfusion ($p < 0.0001$).

Impact of chemotherapy (specific aim # 1 and 2): The severity/extent of RT-associated perfusion defects, as measured visually by the SRS, was greater in the 49 patients who received Dox-based chemotherapy prior to RT, versus those treated with RT alone (Hardenbergh 2001), although the number of evaluable patients at the later follow-up intervals was small. Similarly, patients who received adriamycin (total dose 240-300 mg/m^2) prior to RT had a slightly steeper DRC (i.e., a greater decrease in regional perfusion) than patients treated with RT alone.



Impact of Race: The visual comparison of serial scans by a nuclear medicine radiologist shows an increase in the severity and extent of perfusion defects (SRS) in AA's vs. Caucasians. Similarly, quantitative analysis shows a steeper DRC for AA's than the Caucasians at both 6 and 12 months (6-month data shown below).





Relating changes in regional perfusion to changes in regional and global LV function (specific aim # 3):

Quantitative Data(Wall Motion and Ejection Fraction): The rates of wall motion abnormalities, and declines in EF >= 5%, are shown in the table for the patients with and without perfusion defects. Patients with post-RT perfusion defects appear more likely to have wall motion abnormalities than patients without such defects. The location of the wall motion abnormalities was typically in the anterior region of the heart, corresponding to the area of incidental RT and associated perfusion defects. Overall, the degree of change in EF was similar in the patients with and without perfusion defects. However, using the SRS to define the severity and extent of the perfusion defects, there was a non-significant tread for a larger fraction of the patients with SRS >=5 to have declines in EF >=5%, compared to those with lower SRS. At 6-months, the rates of EF declining >=5% was 3/12 vs. 4/10 in patients with SRS 2-4 and >= 5, respectively. The comparable numbers at 12 and 18 months was 1/9 vs. 3/6, and 2/7 vs. 3/5, respectively.

Some of the non-significant p-values may result from small numbers (low power) rather than the lack of difference. Longer follow-up of these and additional patients is necessary to better define the long-term functional consequences of RT-induced perfusion defects.

Months Post-RT	Wall Motion	Abnormalities		Fraction of	Patients with	EF Decline >= 5%
	No Perfusion Defects	Yes Perfusion Defects	p-value	No Perfusion Defects	Yes Perfusion Defects	p-value
6	5/52	11/25	0.001	8/50	7/22	NS
12	1/37	6/22	0.009	8/36	4/15	NS
18	0/24	1/14	0.37	5/19	5/12	NS
24	0/8	3/12	0.19	5/8	3/9	NS

NS=Not Significant

Clinical Symptoms (chest pain): With a median follow-up of 16 mos. (range 6-24 mos.), 10/83 evaluable patients had at least one episode of transient chest pain, occurring 0-14 mos. (median 6.5 mos.) post-RT. The rates of chest pain in the patients with and without a new perfusion defect were 9/31 and 1/52, respectively (p=0.001). A similar result was found when patients were segregated based on the use of chemotherapy. Cardiology evaluation in these ten cases lead to a diagnosis of pericarditis in two, and the etiology of the pain remains unexplained in eight. None had myocardial infarction or congestive heart failure. Thus, "cardiac" symptoms may occur more frequently in patients with perfusion abnormalities by SPECT after RT than in patients with normal SPECT scans, suggesting that such perfusion defects may be clinically significant. However, other explanations remain possible. Women who know that they have RT-induced perfusion defects may be more likely to seek medical attention for episodes of chest pain. Alternatively, perfusion defects may simply correlate with an increased rate of pericarditis in patients with larger irradiated heart volumes. Since the number of observed episodes of symptoms remains small,

additional follow up with larger numbers of patients will be necessary to better assess the clinical significance of RT-induced perfusion defects.

To explore the ability of 3D treatment planning in designing treatment beams for patients with left-sided breast cancer to achieve a reduction in the volume of the heart receiving radiation compared to a conventional 2D clinical set-up (specific aim #4): In a series of 20 patients, a formal comparison was made between RT fields that were designed using 3D planning software, and RT fields defined using our conventional methods (CT-based, but without 3D planning software). In patients in whom the internal mammary nodes were to be irradiated, there was a suggestion that the 3D planning tools were helpful in minimizing the volume of heart irradiated. In the group of women where the intention was to treat the breast alone, 3D planning was not beneficial.

Difficulties in Accomplishing Tasks:

The preliminary data suggests that there might be an impact of race on the outcome. However, there are a limited number of African American patients evaluable on this study. This will be addressed by enrolling additional AA patients in the future. Some of the patients have elected not to have additional post-RT scans, and this has reduced the number of evaluable patients. The vast majority of patients remain evaluable.

In May of 2001, the primary investigator, Dr. Patricia Hardenbergh, left Duke. Dr. Lawrence Marks, a co-investigator, became the primary investigator. IRB approval was obtained.

Recommended Changes or Future Work:

This work will continue under the recently-approved Clinical Bridge Award. That study will assess the longer-term changes in cardiac perfusion following RT, the possible roles of chemotherapy and race in RT-induced heart injury, and the functional consequences of perfusion changes.

In future work, consideration will be given to using additional imaging modalities of the heart. We would anticipate using serial Magnetic Resonance Imaging (MRI) images to assess for regional micro-vascular cardiac perfusion (similar to what is provided by SPECT) as well as MRI based assessments of the regional inflammation, metabolic activity, and coronary artery blood flow.

Similarly, positron emission tomography (PET) possibly might provide quantitative data relating to regional metabolism in the heart. When this technology is more readily available, we anticipate including serial PET evaluation in these patients. Serial PET scans will be compared to each other, is a similar fashion to how serial SPECT scans are to be analyzed.

Key Research Accomplishments:

- We have established the first dose-response curve for RT-induced perfusion defects in the heart.
- We have defined the time-dependence of these perfusion changes for the first 2 years following RT.
- We have observed that RT-induced cardiac injury might be more prevalent in patients who also receive chemotherapy (vs. RT alone) and in African Americans (vs. Caucasians).
- We have demonstrated that these perfusion defects may be associated with wall motion abnormalities and the development of cardiac dysfunction/symptoms.
- We are showing the importance of sophisticated radiation therapy treatment planning (3-D) for patients with left-sided breast cancer. This may be particularly relevant for patients with left-sided breast cancer who have received chemotherapy.

Reportable Outcomes:

Manuscripts and Abstracts:

Munley MT, Marks LB, Hardenbergh PH, Bentel GC: Functional imaging of normal tissues with nuclear medicine: Applications in radiotherapy. Seminars in Radiation Oncology 11(1):28-36, 2001.

Marks LB, Bentel GC, Hardenbergh PH. Lind PAR, Prosnitz LR. A practical and easy method to locate the first three internal mammary lymph-node bearing areas. Int J Radiat Oncol Biol Phys 50(2)421-425, 2001.

Hardenbergh PH, Munley MT, Bentel GC, Kedem RR, Borges-Neto S, Hollis D, Prosnitz LR, Marks LB. Cardiac Perfusion Changes in Patients Treated for Breast Cancer with Radiation Therapy and Doxorubicin: Preliminary Results. International Journal of Radiation Oncology Biology, Physics 49:1023-1028, 2001.

Hardenbergh PH, Munley MT, Bentel GC, Strickland J, Borges-Neto S, Hollis D, Prosnitz LR, Marks LB: Pathophysiologic impact of doxorubicin (Dox) and radiation therapy (RT) on the heart of patients treated for breast cancer. Proceedings of the 41st Annual ASTRO Meeting. *Int. J. Radiat. Oncol. Biol. Phys.* 45(3) (Suppl):197, 1999.

Hardenbergh PH, Munley MT, Hu CY, Borges-Nesto S, Hollis DR, Marks LB: Breast cancer treatment related mycardial damage appears increased in African-American Women. American Society of Clinical Oncology, Thirty-Seventh Annual Meeting, San Francisco, CA, May 12-15, 2001. ASCO 20 (1 of 2):29a, 2001.

Lind PA, Pagnanelli R, Marks LB, Hu C, Borges-Neto S, Hardenbergh PH. Myocardial perfusion changes in patients treated with left-sided breast cancer and correlation with coronary artery distribution. ASTRO 43rd Annual Meeting, San Francisco, CA, Nov. 3-7, 2001. Int J Radiat Oncol Biol Phys 5(suppl 1):157-158, 2001.

Hardenbergh P, Munley M, Hu C, Hollis D, Light K., Blazing M, Borges-Neto S, Marks L. Doxorubicin-based chemotherapy and radiation increase cardiac perfusion changes in patients treated with left-sided breast cancer. ASTRO 43rd Annual Meeting, San Francisco, CA, Nov. 3-7, 2001. Int J Radiat Oncol Biol Phys 5(suppl 1):158, 2001.

Yu XL, Prosnitz R, Zhou SM, Hardenbergh P, Tisch A, Blazing M, Borges-Neto S, Hollis D, Wong T and Marks L. Symptomatic "cardiac" events following radiation therapy (RT) for left-sided breast cancer: possible association with RT-induced changes in regional perfusion. 25th Annual San Antonio Breast Cancer Symposium. Abstract submitted.

Prosnitz R, Zhou SM, Yu XL, Hardenbergh P, Tisch A, Blazing M, Borges-Neto S, Wong T and Marks L. Long term radiation (RT)-induced cardiac perfusion defects following left sided tangential breast-chest wall irradiation. 25th Annual San Antonio Breast Cancer Symposium. Abstract Submitted

Marks L, Prosnitz R, Zhou SM, Yu XL, Hardenbergh P, Tisch A, Blazing M, Hollis D, Borges-Neto S, Wong T and Marks L. Functionla Consequences of Radiaiton (RT)-induced Perfusion Changes in Patients with Left-Sided Breast Cancer. ASTRO 44th Annual Meeting, New Orleans, Oct 2002. Abstract in press.

Quaranta B, Das S, Light K, Marks L. Non-axial treatment beams orientations can reduce the dose to normal tissues, and thus improve the therapeutic ratio, for lower lobe lung cancers. ASTRO 44th Annual Meeting, New Orleans, Oct 2002. Abstract in press

Funding:

A Clinical Bridge grant has been awarded by the DOD entitled: Treatment-Related Cardiac Toxicity in Patients Treated for Breast Cancer. This study will continue assessing the longer-term changes in cardiac perfusion following RT, the possible roles of chemotherapy and race in RT-induced heart injury, and the functional consequences of perfusion changes.

Clinical Relevance:

- Treatment of left-sided breast cancer may be affected by the results of this study. The development of 3-D treatment planning to limit treatment-induced heart damage may become more widely applied.

- A better understanding of RT-induced cardiac dysfunction (with or without chemotherapy) may help us better plan therapies for women with breast cancer.

- While this study addressed only patients with breast cancer, its findings are applicable to patients with other diseases as well. Recognition of RT-induced cardiac dysfunction, and its dose/volume-dependence, may impact on therapy for patients with cancers of the lung, esophagus, mediastinal tissues and upper abdomen.

Conclusions:

RT induces dose-dependent changes in regional cardiac perfusion within the region of heart irradiated. This suggests that RT may cause microvascular damage to the heart. To date, there have been no clinically-relevant cardiotoxic events observed, and thus the clinical importance of these perfusion changes remains unclear. The incidence of these perfusion defects appears higher in patients who also receive chemotherapy (vs. RT alone) and in African Americans (vs. caucasians). Additional follow-up of the current cohort of patients, plus the study of additional patients, will help determine if these perfusion defects are persistent, if they have long-term clinical significance, and the role of chemotherapy and race in their evolution.

Personnel:

Lawrence Marks, Patricia Hardenbergh, Salvador Borges-Neto, Michael Blazing, Su-Min Zhou, Donna Hollis, Pehr Lind, Andrea Tisch, Stephanie Yu

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REPLY TO
ATTENTION OF:

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Encl

PHYLIS M. RINEHART
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